REMARKS

Status of Claims

Claims 1-33, 39-44, and 51-64 (including all previously withdrawn canceled claims) are canceled.

Claim 34 is amended and new claims 71 and 72 are added.

Support for amendment of claim 34, for new claims 71 and 72, is discussed below.

Accordingly, claims 34-38, 45-50, and 65-72 are currently under consideration.

Amendment of Claims

In view of the rejection of claim 34 for lack of enablement commensurate in scope with the broadest interpretation of the claims, Applicants amend claim 34, and explain support for the amendments as follows:

- claim 35, "wherein the disorder characterized by abnormal cell proliferation is cancer", has been incorporated into claim 34. Claim 35 is thus canceled;

- the amendment "obtaining a suspected cancerous biological tissue ~~test~~ sample from an individual" was made in response to the Examiner's comment that the claim could read on testing any sample, including samples not suspected of being cancerous. Support can be found throughout the specification, e.g., paragraph [0001] teaching that the invention relates to methods, which are especially useful for the detection of tumors and their precursory stages based on the detection of overexpression of human transketolase like-1 gene in biological samples, and, e.g., at paragraph [0163] teaching that the staining procedure was furthermore applied to tissues from breast-, lung-, cervical- (CINIII), gastric-, oesophageal-, endometrial-, ovarian-carcinomas. In all these cases nuclear and cytoplasmic staining for tktl1 could be observed in the cancerous cells;

- support for "obtaining a normal control sample of the same type tissue as as the suspected cancerous biological tissue but known to be non-cancerous" can be found in Example Example 1 which demonstrated that human transketolase like-1 gene is overexpressed in colon carcinoma tissue in comparison to normal colon tissue; and

- support for the amendment of step (g) can be found in the above and paragraph [0001] disclosing that in one aspect the invention relates to methods, which are especially useful for the

detection of tumors and their precursory stages based on the detection of overexpression of human transketolase like-1 gene in biological samples. See also paragraph [0004] "cancer or its precursors".

New claim 71 parallels claim 34 but is not limited to tissue samples, and rather, recites "obtaining a biological test sample suspected to contain cancerous cells from an individual" in order to cover samples other than tissues, e.g., serum, urine, semen, stool, bile, a biopsy or a cell- or tissue-sample as recited in claim 38.

New claim 72 parallels claim 71, but lists the types of biological test samples.

Both claims 71 and 72 also differ from claim 34 in not requiring the tester to conduct the comparative ("normal") test himself, but to consult a previously available comparison value obtained by running the same required test.

Invention

The invention relates to the recognition of the link between:

(a) overexpression of transketolase like-1 gene (TKT-L1; TKR) and

(b) disorders characterized by abnormal cell proliferation.

In practical terms, the present invention makes it possible to detect disorders characterized by abnormal cell proliferation – and more specifically, tumors and their precursory stages. This is done by detecting overexpression of transketolase like-1 gene in a biological sample. To test for "overexpression" it is of course necessary to know the "normal" level of expression, and this is either known or determined using a corresponding but non-cancerous sample.

Objection

Claim 44 is objected to under 37 CFR 1.75(c), for failing to further limit the subject matter of a previous claim.

In response, Applicants cancel claim 44.

Claim Rejections - 35 USC § 112

Claims 34-38, 44-50, and 65-70 are rejected under 35 U.S.C. §112, first paragraph, because the specification,

- while being enabling for an *in vitro* method for detecting carcinoma tissue in an individual comprising detecting in a tissue sample obtained from said individual the level of polynucleotides comprising SEQ ID NO:1 and comparing said level to the level of polynucleotides comprising SEQ ID NO:1 in a corresponding control tissue sample from a healthy subject, wherein a higher level of polynucleotides comprising SEQ ID NO:1 in the tissue sample from the individual as compared to said control tissue sample indicates that the tissue sample from the individual comprises carcinoma tissue,

- it does not reasonably provide enablement for an *in vitro* method for detecting every type of disorder characterized by abnormal cell proliferation ..., wherein a higher level of detected polynucleotides in the biological test sample as compared to the level of detected polynucleotides in the normal control samples indicates that said individual has at least one of any disorder characterized by abnormal cell proliferation.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant claims are drawn to an *in vitro* method for detecting every type of disorder characterized by abnormal cell proliferation in an individual comprising detecting in just any biological sample obtained from said individual and just any normal control sample. This includes methods wherein just any samples are used and methods wherein every disorder characterized by abnormal cell proliferation, including those characterized by having either increased or decreased proliferation, is detected.

The specification teaches an *in vitro* method for detecting carcinoma tissue in an individual ... wherein a higher level of polynucleotides comprising SEQ ID NO:1 in the tissue sample from the individual as compared to said control tissue sample indicates that the tissue sample from the individual comprises carcinoma tissue (see Example 2, in particular). Carcinomas disclosed as overexpressing polynucleotides comprising SEQ ID NO:1 include those of colon, lung and stomach (see Example 2). However, the specification does not demonstrate that polynucleotides comprising SEQ ID NO:1 are overexpressed in tissue from a patient with a carcinoma other than the carcinoma tissue. Further, the specification does not demonstrate that polynucleotides comprising SEQ ID NO:1 are overexpressed in any disorders characterized by abnormal cell proliferation other than carcinomas. Disorders characterized by abnormal cell

proliferation include pre-neoplasia, giomeruionephritis, benign prostate hyperplasia, and psoriasis. Further, the specification does not demonstrate that polynucleotides comprising SEQ ID NO:1 functionally regulate proliferation.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to an in vitro method for detecting every type of disorder characterized by abnormal cell proliferation in an individual ..., and Applicant has not enabled said method because it has not been shown that a higher level of detected polynucleotides that hybridize to a probe that is at least 80% identical to a part of at least 15 consecutive nucleotides of SEQ ID NO:1 or is complementary or reverse complementary to such a part and wherein said probe hybridizes under stringent conditions to SEQ ID NO:1 but does not hybridize to an other transketolase or transketolase like sequence in just any sample from an individual as compared to the level of detected polynucleotides that hybridize to a probe that is at least 80% identical to a part of at least 15 consecutive nucleotides of SEQ ID NO:1 or is omplementary or reverse complementary to such a part and wherein said probe hybridizes under stringent conditions to SEQ ID NO:1 but does not hybridize to an other transketolase or transketolase like sequence in just any control sample is indicative of every disorder characterized by abnormal cell proliferation. In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Applicants Response

In response, Applicants have carefully amended claim 34, and added new claims 71 and 72 to address each of the concerns raised by the Examiner.

1. The type of abnormal cell proliferation has been limited to cancer.

2. The "test sample" has been limited in claim 34 to a suspected cancerous biological tissue. As the entire specification is directed to detection of cancer, the first step of obtaining a "test sample" has been amended, in claim 34, to "obtaining a suspected cancerous biological tissue ~~test~~ sample from an individual". While Applicants believed the nature of the sample to have been implicit in the claims, the current amendment makes this explicit.

New claim 71 parallels claim 34 but instead of "tissue samples" (the term "tissue" requiring cells to be interconnected) recites "obtaining a biological test sample suspected to contain cancerous cells from an individual" in order to cover samples other than tissues, e.g., serum, urine, semen, stool, bile, a biopsy or a cell- or tissue-sample as recited in claim 38.

New claim 72 parallels claim 71, but expressly lists the types of biological test samples as recited in claim 38.

In addition to the specification teaching that it is well known to obtain samples from non-tissue such as blood and urine, Applicants attach hereto three references. Two discuss circulating tumor cells in blood, the third discusses detection of bladder cancer cells in urine.

3. Regarding the Examiner's position that the disclosure is limited to carcinoma, Applicants acknowledge that the figures and associated text use carcinomas by way of example, but the disclosure is not so limited, and Applicants should not be limited to the illustrated examples. As the Examiner may be aware, tumor tissue can be divided in two subgroups

(I) containing invasive tumor cells which might develop metatstasis = cancer = cancerous tissue (with the sub-sub-group carcinoma), and

(II) consisting of non-invasive tumor cells = (benign) tumor.

No technical reason has been raised for the Examiner to doubt that the test for cancer, demonstrated in great detail with carcinomas but also discussed with other cancers, is not applicable to other cancers, particularly in view of Applicants own disclosure. The Examiner is referred to paragraph [0012] "The present invention is based on the inventor's findings, that human transketolase like-1 gene as given in SEQ. ID. 1 (cf. TKT-L1, TKR: NM.sub.--012253; Accession number: X91817) is highly overexpressed in tissue of colon carcinoma, pancreatic carcinoma, lung cancer and gastric cancer compared to the level found in respective normal control tissue." See also paragraph [0081] "In a preferred embodiment the tumor is for example cancer of the of the head and the neck, cancer of the respiratory tract, cancer of the gastrointestinal tract, cancer of the skin and its appendages, cancer of the central and peripheral nervous system, cancer of the urinary system, cancer of the reproductive system, cancer of the endocrine system, cancer of the soft tissues and bone, cancer of the hematopoietic and lymphopoietic system.

Applicants explain the results reported in Example 2: Ten suspected cancerous colon tissue probes were received from the pathology and were tested according to the method of claim 34. Only one of the probes showed an overexpression of TKTL1. That means: only in that single case the suspicion of cancer was confirmed; in the other nine cases the suspicion was not confirmed, i.e, these probes turned out to be merely tumorous (benign) but not cancerous.

Five suspected lung adenocarcinoma tissue probes were received from the pathology and were tested according to the method of claim 34. Two of these probes showed an overexpression of TKTL1. Result: For these two tissue probes the suspicion of cancer was confirmed, in the other three cases the suspicion was not confirmed, i.e these probes turned out to be merely tumorous (benign) but not cancerous.

Finally, five suspected cancerous tissue probes of the stomach were received from the pathology and were tested according to the method of claim 34. Three of these probes showed an overexpression of TKTL1. Result: For these three tissue probes the suspicion of cancer of the stomach was confirmed, in the other two cases the suspicion was not confirmed, i.e these probes turned out to be merely tumorous (benign) but not cancerous.

For the information of the Examiner, Applicant Langbein et al., teaching in extensive detail how the experimentation done in Example 2 was carried out.

4. Regarding the identity of the normal control sample, this is clarified in claim 34 as the same type tissue as as the suspected cancerous biological tissue but known to be non-cancerous. See Example 1 which demonstrated that human transketolase like-1 gene is overexpressed in colon carcinoma tissue in comparison to normal colon tissue.

In view of the foregoing, reconsideration and withdrawal of all rejections and allowance of the application is respectfully solicited.

If the Examiner believes that a telephone conversation with the Applicant's attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at the telephone number shown below.

The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of

this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 16-0877.

Respectfully submitted,

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